R E M A R K S

Telephone Interview with the Examiner

The undersigned had a telephone interview with Examiner Huang on January 7, 2010.

Pursuant to 37 CFR 1.133(b), applicants provide the following summary of the aforesaid telephone interview.

1. Examiner Huang said that her comment in the September 28, 2009 Office Action that "the intended use of a composition does not have patentable weight in a composition claim" was intended to mean that the use in Azuma et al. (i.e., the treatment of glaucoma) is the same use as recited in applicants' claims.

2. The undersigned asked Examiner Huang if there would be a better chance of obtaining allowance for method claims (which are presently withdrawn) than for the presently examined composition claims.

a. Examiner Huang said she could not give a definite answer to this question, since she did not examine the method claims, because the method claims were not elected and were withdrawn from consideration.

b. Examiner Huang noted that the present withdrawn method claim 5 was broader than the present agent claims in that the agent claims recite a specific Rho kinase inhibitor ((R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide,

whereas the present method claim 5 recites "a Rho kinase inhibitor" (i.e., any Rho kinase inhibitor).

c. Examiner Huang said that the present method claims do not appear to recite features which would patentably distinguish over Azuma et al.

Claim Objection

In item no. 7 at the bottom of page 2 of the Office Action, the position was taken that claims 1 and 2 are substantially duplicate claims.

Claim 2 was canceled hereinabove.

Withdrawal of the claim objection is respectfully requested.

Claim Amendments

The feature of claim 13 was introduced into claim 1.

Claims 2, 3 and 13 were canceled.

Obviousness Rejection Under 35 USC 103

Claims 1 to 2 and 4 to 13 were rejected under 35 USC 103 as being unpatentable over Azuma et al. (WO 00/09162) for the reasons set forth in item no. 8 beginning on page 3 and continuing to page 4 of the Office Action.

It was stated in the enclosed Office Action that USP 6,673,812 would be used as a translation of WO 00/09162.

It was admitted in the Office Action that Azuma et al. do not expressly teach a composition comprising the combination of a Rho kinase inhibitor and a beta-blocker.

Arguments in Support of Patentability
of the Presently Claimed Invention

1. Azuma et al. do not teach or suggest a composition comprising a combination of timolol and (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide (hereinafter sometimes referred to as "Y-39983") as recited in applicants' present claim 1. In fact, Azuma et al. merely disclose a composition for glaucoma comprising a Rho kinase inhibitor (such as (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide) as a sole active ingredient. Azuma et al. do not each or suggest a composition comprising a combination of a Rho kinase inhibitor and another anti-glaucoma agent.

It was alleged at the bottom of page 3 of the Office Action that Azuma et al. teach a combination therapy and that each of a Rho kinase inhibitor and a beta-blocker are useful for glaucoma. Applicants respectfully submit that Azuma et al. do not teach or suggest that a combination therapy is useful for glaucoma. In contrast thereto, Azuma et al. teach that the use of β-blockers

is limited due to their side effects (see Azuma et al., column 1, lines 44 to 50). Therefore, from the disclosure in Azuma et al., it is respectfully submitted that one of ordinary skill in the art would consider that β-blockers including timolol would be an undesirable therapeutic agent for treating glaucoma.

In view of the above, applicants respectfully submit that Azuma et al. fail to teach or suggest a combination of (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide and timolol as recited in applicants' present claim 1.

2. Azuma et al. teach that there are some problems (e.g., side effects) of the previous therapeutic agents for treating glaucoma, and aim at solving these problems (see Azuma et al., column 2, lines 24 to 27). That is, Azuma et al. teach an agent for treating glaucoma (an Rho kinase inhibitor) in order to avoid using the previous therapeutic agents for treating glaucoma (e.g., timolol).

Therefore, it is respectfully submitted that a person of ordinary skill in the art would not consider to combine a Rho kinase inhibitor, such as (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide and a beta-blocker, such as timolol. Stated differently, it is respectfully submitted that Azuma et al. teach away from the presently claimed invention.

3. The following position was taken on page 4, lines 11 to 14 of the Office Action:

> "One of ordinary skill in the art would have been motivated to do this [combine a Rho kinase inhibitor and a beta blocker] because it is desirable to have and produce a composition comprising many components which have desirable effects for the condition resulting in the additive effect of the ingredients for glaucoma" [emphasis supplied]

For the reasons discussed hereinabove, it is respectfully submitted that Azuma et al. do not teach to combine a Rho kinase inhibitor and a beta-blocker.

Furthermore, applicants respectfully submit that applicants' experimental data of record demonstrate a synergistic effect for reducing intraocular pressure ("IOP") for applicants' presently claimed composition comprising (R)-(+)-N-(1H-pyrrolo[2,3,-b]pyridin-4-yl-4-(1-aminoethyl)benzamide and timolol.

(a) For the following reasons, applicants respectfully disagree with the allegation in the Office Action on page 6, lines 1 to 5 that all the comparison results of record demonstrate only an "additive effect," rather than a "synergistic effect."

Reproduced hereinbelow is Table 1 in the DECLARATION UNDER 37 CFR 1.132 of Masakazu HATANO dated July 21, 2009 (hereinafter referred to as the "July 21, 2009 HATANO DECLARATION").

Table 1 IOP reduction from initial IOP after administration of Y-39983 and timolol in combination as the difference from the control group

	Time after instillation			
	0hr	1hr	2hr	4hr
①Single administration group of Y-39983	0	-0.9 mmHg	1.2 mmHg	-0.2mmHg
②Single administration group of timolol	0	1.8 mmHg	3.7 mmHg	1.4 mmHg
③Y-39983 and timolol combination administration group	0	3.1 mmHg	5.5 mmHg	3.3 mmHg
Theoretical additive IOP reduction (①+②)	0	1.1 mmHg	4.9 mmHg	1.2 mmHg

As apparent from the above Table 1, the actual IOP reduction of the combination of Y-39983 and timolol 4 hours after instillation (3.3 mmHg) is substantially greater than the theoretical additive IOP reduction (1.2 mmHg). Also, it is noted that the IOP reduction of said combination 1 and 2 hours after instillation (3.1 and 5.5 mmHg, respectively) is greater than each theoretical additive IOP reduction (1.1 and 4.9 mmHg, respectively). That is, the combination of Y-39983 and timolol exhibits more than an additive effect (i.e., a synergistic effect) at each of 1 hour, 2 hours and 4 hours after instillation.

4. The following position was taken on page 5, lines 16 to 20 of the Office Action:

> "Applicant refers to the comparative in the Hatano declaration as evidence that HA1077 and timolol are not synergistic and argues that the combination does not show persistence of action at 4 hours which is not persuasive as the combination of the HA1077 and timolol as addressed by Applicant did exhibit an additive effect 1-2 hours after instillation. Whereby there is an additive effect and supports the fact that there is a reasonable expectation of success to combine these two categories of agents." [emphasis supplied]

For the following reasons, applicants respectfully disagree with the above position.

Azuma et al. disclose a composition for treating glaucoma comprising a Rho kinase inhibitor, wherein the Rho kinase inhibitor may be any compound as long as it has a Rho kinase inhibitory activity (see Azuma et al., column 8, line 66 to column 9, line 1). That is, Azuma et al. teach that every Rho kinase inhibitor reduces IOP in the same manner. Despite this teaching, it was shown in Table A in the July 21, 2009 HATANO DECLARATION that the combined combination use of timolol and a Rho kinase inhibitor other than the Rho kinase inhibitor recited in applicants' present claims Y39983, namely, 1-(5-

isoquinolinesulfonyl)-homopiperazine (referred to hereinafter as "HA1077"), does not reduce IOP in a synergistic manner.

Table A in the July 21, 2009 HATANO DECLARATION is reproduced as follows:

Table A IOP reduction from initial IOP after administration of HA1077 and timolol in combination as the difference from the control group

	Time after instillation			
	0hr	1hr	2hr	4hr
①Single administration group of HA1077	0	1.0 mmHg	1.2 mmHg	0.1 mmHg
②Single administration group of timolol	0	2.3 mmHg	1.9 mmHg	1.6 mmHg
③HA1077 and timolol combination administration group	0	3.2 mmHg	2.7 mmHg	0.9 mmHg
Theoretical additive IOP reduction (①+②)	0	3.3 mmHg	3.1 mmHg	1.7 mmHg

As apparent from the above Table A, the IOP reduction of the combination of HA1077 and timolol 1, 2 and 4 hours after instillations (3.2 mmHg, 2.7 mmHg and 0.9 mmHg, respectively), were smaller than each theoretical additive IOP reduction (3.3 mmHg, 3.1 mmHg and 1.7 mmHg, respectively). That is, the combination of HA1077 and timolol reduced IOP in a partially additive manner. HA 1077 is known to have a Rho kinase inhibitory activity (see the paragraph bridging pages 4 and 5 of the present specification).

These findings indicate that every combination of a Rho kinase inhibitor and a β-blocker does not necessarily exhibit a synergistic effect. That is, the presently claimed invention shows unpredictable results (i.e., a synergistic effect).

It is respectfully submitted that based on the disclosure in Azuma et al., one of ordinary skill in the art would not arrive at the discovery that the combination of (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl-4-(1-aminoethyl)benzamide and timolol provides unpredictable and synergistic results.

5. Applicants disagree with the following allegations set forth in the "Response to Arguments" in item no. 9 on pages 4 to 6 of the Office Action.

a. Applicants disagree with the allegation in the Office Action that the "recitation of intended use does not have

patentable weight in a composition claim" (see the middle of page 5 of the Office Action).

The Examiner's attention is directed to In re Sullivan, 84 USPQ2d 1034, 1039-1040 (Fed. Cir. 2007) which held as follows:

> "The Board failed to consider each of these declarations. The Board stated in a footnote that the declarations of record relate only to the use of the claimed composition as an anti-venom, and thus the Board expressly declined to give any meaningful consideration to them. *Sullivan*, No. 2006-0220, slip op. at 13 n.7. As stated above, when an applicant puts forth relevant rebuttal evidence, as it did here, the Board must consider such evidence. The claimed composition cannot be held to have been obvious if competent evidence rebuts the prima facie case of obviousness. By failing to consider the submitted evidence, the Board thus committed error.
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> * * *
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> Moreover, the Board was mistaken to assert that the declarations only relate to the use of the claimed composition. The declarations do more than that; they purport to show an unexpected result from use of the claimed composition, how the prior art taught away from the composition, and how a long-felt need existed for a new antivenom composition. While a statement of intended use may not render a known composition patentable, the claimed composition was not known, and whether it would have been obvious depends upon consideration of the rebuttal evidence. Had the Board considered or reviewed the declarations in any meaningful way, it might have arrived at a different conclusion than it did.

> Furthermore, the Board's focus on the intended use of the claimed composition misses the mark. The board cites *In re Zierden*, 411 F.2d 1325 [162 USPQ 102] (CCPA 1969), for the proposition that a statement of a new use for an otherwise old or obvious composition cannot render a claim to the composition patentable. In that case, applicant conceded that his composition was distinguished from the composition disclosed in a prior art patent only by the statement of intended use. Our predecessor court held that the intended use for the known composition could not render the claim patentable. In this case, applicant does not concede that the only distinguishing factor of its composition is the statement of intended use and, in fact, extensively argues that its claimed composition exhibits the unexpected property of neutralizing the lethality of rattlesnake venom while reducing the occurrence of adverse immune reactions in humans. Such a use and unexpected property cannot be ignored. See *In re Papesch*, 315 F.2d 381, 391 [137 USPQ 43] (CCPA 1963) ("From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing....There is no basis in law for ignoring any property in making such a comparison."). The issue here is not whether a claim recites a new use, but whether the subject matter of the claim possesses a unexpected use. That unexpected property is relevant and thus the declarations describing it should have been considered by the Board."

b. At the middle of page 5 of the Office Action, the position was taken that "recitations of <u>desired results</u> do not materially change the components in a composition claim."

As discussed hereinabove, it is improper to ignore "intended use" for a composition claim. Moreover, as discussed hereinabove, applicants have provided a showing of unexpected and synergistic results which also should not be ignored.

c. It was alleged at the middle of page 5 of the Office Action that "combination therapy is addressed by Azuma and is well-known in the art for glaucoma treatment."

As discussed hereinabove, Azuma et al. do not teach or suggest combining a Rho kinase inhibitor and a beta-blocker for treating glaucoma. Furthermore, the disclosure of Azuma et al. would not lead one of ordinary skill in the art to expect the synergistic results provided by the presently claimed invention.

d. It was alleged on page 5 of the Office Action that Azuma et al. teach that there would be a reasonable expectation of success in combining timolol and Y-39983 for treating glaucoma.

As discussed hereinabove, Azuma et al. teach away from using a beta-blocker such as timolol. Moreover, as discussed above, Azuma et al. do not teach combining a Rho kinase inhibitor with any other agent for reducing glaucoma.

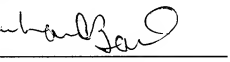
e. Concerning the position set forth on page 6, lines 1 to 5 of the Office Action, it has been demonstrated hereinabove that the presently claimed invention provides synergistic results.

Withdrawal of the 35 USC 103 rejection is therefore respectfully requested.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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Enc.: PETITION FOR EXTENSION OF TIME